## REMARKS

### Status of the Claims

Claims 1-7 are pending. Claims 1, 3, 5, and 7 are amended to clarify the claims. Support for the amendments can be found throughout the specification as originally filed. Support for amended claim 1 can be found, for example on page 7 lines 24-25 of the published PCT application (all citations to the published application herein are based on the corresponding published PCT application, WO 2005/080603). The amendments to claims 5 and 7 are supported, for example, on page 11, lines 9-12. Thus, the amendments do not constitute new matter.

### Drawing Objections

Figures 1-6 were objected to as lacking the proper labels and as containing shading of poor quality and lines which are not clean and well defined. A set of amended drawings (Figures 1-6) are submitted herewith, thereby obviating the objection. Applicants respectfully request reconsideration and withdrawal of the objection.

### Rejections under 35 USC §112, second paragraph

The patent office rejected claims 1-7 under 35 USC §112, second paragraph. Under 35 USC §112, second paragraph, the specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention. Claims 1-7 are rejected as being indefinite based on the following assertions:

**(a)** Claim 1 was rejected as indefinite based on the assertion that one of skill in the art would not understand what is meant by a "molecular motor." Applicants traverse this rejection, but have nonetheless amended the claim, and respectfully request reconsideration and withdrawal of the rejection.

**(b)** Claim 1 was rejected as indefinite based on the assertion that one of skill in the art would not understand what is meant by "directly adjacent." Applicants traverse this rejection, as the specification clearly defines the phrase "directly adjacent" on page 4, lines 5-8 of the published PCT application. Thus, Applicants respectfully request reconsideration and withdrawal of the rejection.

**(c)** Claim 1 was rejected as indefinite based on the assertion that one of skill in the art would not understand what is meant by "detection probe." Applicants traverse this rejection. Those of skill in the molecular biology arts are well versed in the use of detection probes to allow visualization of molecular binding events, and would clearly understand the use of a detection probe in the claimed invention. Furthermore, the specification discloses that a detection probe can be anything capable of attaching to the affinity tag on the second target-specific nucleic acid and providing a means of detecting the movement generated by the molecular motor (page 10, lines 1-10), and provides a list of exemplary detection probes. Finally, specific examples of such detection probes and their use in the methods of the invention are provided on page 14 lines 14-18; page 15 lines 29-32; page 19 line 15 to page 20 line 28(*See* page 19, lines 15-33). Based on the knowledge of those of skill in the art in light of the detailed guidance regarding detection probes and their use, those of skill in the art would clearly understand what is meant by "detection probe", and Applicants respectfully request reconsideration and withdrawal of the rejection.

**(d)** Claims 5 and 6 are rejected as indefinite based on the assertion that one of skill in the art would not understand what is meant by "an elemental metal nanorod." Applicants traverse this rejection, but have nonetheless amended the claim to recite "metal nanorod" (a non-narrowing amendment). Those of skill in the art clearly understand the meaning of "metal nanorod", and the specification provides specific guidance on metal nanorods, their preparation, and their use in the methods of the invention (see, for example, page 19 lines 15-33 and page 20 lines 15-28). Thus, Applicants respectfully request reconsideration and withdrawal of the rejection.

**(e)** Claim 7 is rejected as incomplete based on the assertion that the detection probe in claim 1 is not defined as having any property that would result in the production of light or the oscillation of intensity of light. Applicants traverse this rejection, but have nonetheless amended the claim to depend from claim 5, to incorporate the limitation that the detection probe is a metal nanorod. Metal nanorods can be used, for example, with visible light to detect movement (*See* page 11, lines 9-11). To detect movement, the nanorod scatters light which results in the oscillation of intensity of light (*See* page 11, lines 11-23). Thus, Applicants respectfully request reconsideration and withdrawal of the rejection.

**Rejections under 35 USC §112, first paragraph**

Claims 1-7 stand rejected under 35 USC §112, first paragraph, based on the assertion that Applicants were not in possession of the invention at the time of filing the application. Applicants traverse the rejection.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, *e.g.*, *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116. M.P.E.P. § 2163(I). An applicant can show possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwoor v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was ready for patenting such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406; *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991).

The description needed to satisfy the requirements of 35 USC §112 "varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence." *Capon v. Eshhar*, 418 F.3d at 1357, 76 USPQ2d at 1084; M.P.E.P. § 2163(I). Thus, an inventor is not required to describe every detail of his invention when one skilled in the relevant art would understand what is intended and know how to carry it out. See, e.g., *In re Hayes Microcomputer Products, Inc. Patent Litigation*, 982 F.2d 1527, 1534-35, 25 USPQ2d 1241, 1246 (Fed. Cir. 1992); M.P.E.P. § 2163.

There is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976).

Currently pending claim one reads as follows:

> A method for detecting a target nucleic acid comprising:
> (a) providing first and second target-specific nucleic acids, wherein the first and second target-specific nucleic acids each comprise sequences complementary to the target nucleic acid; wherein the first target specific

nucleic acid is bound to a first affinity tag and the second target-specific nucleic acid is bound to a second affinity tag, wherein the first affinity tag is capable of binding to a molecular motor, wherein the molecular motor comprises a biological or synthetic molecule capable of induced translational or rotational movements that are capable of detection, and wherein the second affinity tag is capable of binding to a detection probe;

(b) contacting the first and second target-specific nucleic acids to a sample under conditions whereby the first and second target-specific nucleic acids will hybridize to the target nucleic acid if the target nucleic acid is present in the sample, wherein upon hybridization to the target nucleic acid the first and second target-specific nucleic acids are directly adjacent to each other;

(c) ligating the first and second target-specific nucleic acids together;

(d) binding the molecular motor to the first affinity tag and the detection probe to the second affinity tag;

(e) inducing movement of the molecular motor; and

(f) detecting movement of the molecular motor through the detection probe, wherein the movement of the molecular motor serves to detect the target nucleic acid in the sample.

As noted in the specification on page 2, beginning at line 24, "The methods disclosed herein detect a DNA target as the result of ligation with two target-specific nucleic acids, which are ligated only in the presence of the nucleic acid target. The thus-ligated product is used to bridge a molecular motor and a detection probe." Such methods were not known in the prior art, and provide for extremely sensitive and specific detection, as detailed, for example, on page 26 lines 22-30 of the application.

Pending claim 1 is an original claim (amended only to expressly recite the definition for molecular motor that was in the specification as filed). Thus, as noted in *In re Wertheim*, there is a strong presumption that the specification provides an adequate written description of the invention of claim 1.

Furthermore, as noted above, Applicants are not required to describe details of the claimed invention already in the possession of those skilled in the art. Nonetheless, Applicants provide extensive disclosure for each step of the claimed invention. For example:

**(a)** Those of skill in the art of molecular biology are well versed in identifying target nucleic acids that they wish to detect. **Regardless of the nucleic acid sequence of such targets**, it is well within the level of those of skill in the art to design target-specific nucleic acids complementary to the target. Thus, there is no need for Applicants to disclose a series of specific nucleic acid targets and

corresponding target-specific nucleic acids, as this is well within the level of those of skill in the art. Nonetheless, the specification provides a specific example of a nucleic acid target and corresponding target-specific nucleic acids (see page 16 lines 20-27).

**(b)** Those of skill in the art of molecular biology are well versed in molecular motors. Furthermore, the specification defines a molecular motor (*See* page 7, lines 24-29) and provides extensive examples of such motors by GenBank Accession number (*See* Table 1). Furthermore, a specific example for such a molecular motor, its preparation, and its use in the methods of the invention, is provided in example 3 (*See* page 17, lines 19 to page 19 line 2, and page 22 line 27 to page 23 line 24).

**(c)** Those of skill in the molecular biology arts are well versed in the use of detection probes to allow visualization of molecular binding events. Furthermore, the specification discloses that a detection probe can be anything capable of attaching to the affinity tag on the second target-specific nucleic acid and providing a means of detecting the movement generated by the molecular motor (page 10, lines 1-10), and provides a list of exemplary detection probes. Finally, specific examples of such detection probes and their use in the methods of the invention are provided on page 14 lines 14-18; page 15 lines 29-32; page 19 line 15 to page 20 line 28(*See* page 19, lines 15-33).

**(d)** Those of skill in the art of molecular biology are well versed in the optimizing conditions for hybridization by varying the nucleic acid probe sequence and length, reaction buffer, reaction temperature and reaction time. Further, the specification provides guidance on such conditions at page 5 line 21 to page 7 line 23, as well as specific examples on page 16 line 20 to page 17 line 17.

**(e)** Those of skill in the art of molecular biology are well versed in the use of DNA ligases to ligate two nucleic acids together. Further, the specification provides guidance in the use of ligases in the methods of the invention on page 5 line 21 to page 7 line 23, and provides specific examples on page 16 line 20 to page 17 line 17.

**(f)** Those of skill in the art of molecular biology are well versed in the use of affinity tags to directly and indirectly bind two molecules together. It is also well known in the art of molecular biology that an affinity tag can have a specific affinity to a specific target. Further, the specification provides guidance in affinity tags and their use in the methods of the invention on page 4 line 12 to page 5 line 16, as well as

on page 15 (lines 9-15 and 23-32), and provides specific examples on page 16 lines 29-30; page 17 line 26 to page 19 line 3; page 20 line 1 to page 23 line 15.

**(f)** Those of skill in the art of molecular biology are well versed in inducing and detecting movement of molecular motors, and the specification provides guidance for the use of molecular motors in the present invention on page 10 lines 11-26 (inducing) and page 10 line 27 to page 12 line 4 (detecting). Furthermore, the specification provides specific examples on page 22 line 14 to page 23 line 15 (inducing), and page 23 lines 17-33; page 25 line 20 to page 26 line 11 (referring to Figure 5) (detecting).

Thus, based on the bias for adequate written description for claims as originally filed, in light of the knowledge of those of skill in the art, and in light of the extensive guidance presented on the present application, Applicants submit that it would be clear to those of skill in the art that Applicants were in possession of the invention at the time of filing, and therefore Applicants request withdrawal of the rejection under 35 U.S.C. §112, first paragraph the written description requirement.

**Rejections under 35 USC §112, first paragraph**

The patent office rejected claims 1-7 under 35 USC §112, first paragraph, based on the assertion that the specification does not enable one skilled in the art to practice the claimed invention. Specifically, it appears to be the Patent Office's position that the claims are not enabled because the claims encompass the detection of "any and all manner of nucleic acids, including simultaneous detection of an infinite number of nucleic acids that have differing binding specificities." Further, the Patent Office asserts that the method of claim 1 requires only "to employ a first and second nucleic acid and that a 'detection probe' is to bind the second nucleic acid via an affinity tag." Applicants traverse this rejection.

Pending claim 1 is recited above. The Patent Office's analysis clearly ignores at least the following limitations of pending claim 1 (virtually the entire claim):

(a) *"...the first and second target-specific nucleic acids each comprise sequences complementary to the target nucleic acid..."* This clause clearly refutes the Patent Office's assertions, as the first and second target-specific nucleic acids are limited to those that are complementary to the target (and thus "specific"), and thus

are not "any and all manner of nucleic acids, including …an infinite number of nucleic acids that have differing binding specificities."

(b) *"...the first target specific nucleic acid is bound to a first affinity tag .... wherein the first affinity tag is capable of binding to a molecular motor, wherein the molecular motor comprises a biological or synthetic molecule capable of induced translational or rotational movements that are capable of detection..."*

(c) "…wherein upon hybridization to the target nucleic acid the first and second target-specific nucleic acids are directly adjacent to each other…" This clause clearly refutes the Patent Office's assertions, as the first and second target-specific nucleic acids are limited to those that are complementary to the target and that are directly adjacent to each other when hybridized to the target nucleic acid.

(d) *"…ligating the first and second target-specific nucleic acids together..."*

(e) *"...binding the molecular motor to the first affinity tag and the detection probe to the second affinity tag..."*

(f) *"...inducing movement of the molecular motor..."*

(g) *"...detecting movement of the molecular motor through the detection probe, wherein the movement of the molecular motor serves to detect the target nucleic acid in the sample..."*

As discussed at length in the discussion relating to written description, each of these steps in the method is supported by extensive discussion in the specification as filed, both with general guidance and specific examples. Those of skill in the art routinely identify nucleic acid targets of interest, and designing target-specific nucleic acid hybridization probes is well within the level of those of skill in the are; thus, the present method is not limited by any specific target sequence, while the target-specific nucleic acids are limited only by their complementarity to (and specificity for) the target, as well as the requirement that upon hybridization to the target nucleic acid the first and second target-specific nucleic acids are directly adjacent to each other. Given the level of skill in the art, in light of this extensive disclosure, the specification clearly teaches those of skill in the art to make and use the claimed invention.

The Patent Office further asserted that the specification fails to disclose (a) removal of non-hybridized nucleic acids or any other component; (b) the use of a

control to determine if any signal is informative; (c) detection of multiple target nucleic acids in a simultaneous manner; and (d) fails to disclose first and second target-specific nucleic acids that hybridize directly adjacent to one another on any and all manner of target nucleic acids. We address each of these in turn.

**(a)** The Office asserts that the specification fails to disclose removal of non-hybridized nucleic acids or any other component. The Office asserts that absent some means for removal of non-hybridized nucleic acids or the removal of any other component, the signal produced will not be informative.

The claimed method for detection works by detecting the movement of the molecular motor through the detection probe, wherein the movement of the molecular motor serves to detect the target nucleic acid. The claimed method will detect movement through the detection probe only when the first and second nucleic acids are ligated (*See* page 10, lines 20-26). Since ligation is dependent upon specific hybridization of the target specific nucleic acids and the target nucleic acid, movement of the molecular motor and detection by the detection probe will only occur in the presence of the target nucleic acid (*See* page 2, lines 24-31and page 7, lines 6-9). Target nucleic acids that are not hybridized to target specific nucleic acids or any other component that is not part of a nucleic acid bridge, will not generate detectable movement. Therefore, the removal of non-hybridized nucleic acids or removal of any other component is not required to allow for detection of a target nucleic acid.

**(b)** The Office asserts that the specification fails to disclose the use of a control to determine if any signal is informative. As noted above, since ligation is dependent upon specific hybridization of the target specific nucleic acids and the target nucleic acid, movement of the molecular motor and detection by the detection probe will only occur in the presence of the target nucleic acid, and after ligation of the first and second target-specific nucleic acids. Examples of controls are disclosed in the specification *inter alia* in Examples 3.5 and 3.6 and Figures 3 and 5. Furthermore, the design of appropriate controls is well known to those of skill in the art, and thus it is well within the level of those of skill in the art, in light of the specification, to design any control for the methods as deemed appropriate.

**(c)** The Office asserts that the specification fails to disclose how detection of multiple target nucleic acids can be achieved. This is clearly incorrect. Example 2 provides an example of simultaneous detection of multiple targets. On page 15 lines

1-6, the specification notes that gold nanorods of different lengths can be used as detection probes, as the length determines the wavelength of light scattered from it; the example goes on to discuss derivatizing the different nanorods with different affinity tags, for use in detection of different targets. As noted on page 15 lines 17-18 "Observation of ATP-dependent rotation of different colored nanorods indicates the presence of the corresponding target." Furthermore, on page 15 line 20 to page 16 line 5, the disclosure teaches immobilizing differentially modified molecular motors at different locations on a surface, wherein each differentially derivatized molecular motor ultimately is used in detection of a different target nucleic acid. As stated on page 16 lines 4-5 "Observation of ATP-dependent rotation at different locations on the cover slip indicates the presence of the corresponding target nucleic acid." Thus, the Patent Office's assertion on this matter is inaccurate.

**(d)** The Office asserts that the specification "fails disclose first and second target-specific nucleic acids that hybridize 'directly adjacent' to one another on any and all manner of target nucleic acids..." Applicants note that this statement clearly indicates a misunderstanding of the claimed invention. There is no requirement that the first and second target-specific nucleic acids hybridize directly adjacent to one another on all target nucleic acids. In fact, the target-specific nucleic acids are specific by virtue of their complementarity (as well as the first and second target-specific nucleic acids binding to the target so that they are directly adjacent) to only the target nucleic acid being analyzed. In other words, the target-specific nucleic acids will be different for each target (as implied by the name "target-specific"). Thus, it will be clear that Applicants have no obligation to teach "first and second target-specific nucleic acids that hybridize directly adjacent to one another on all target nucleic acids", as this is not part of the present invention.

Thus, based on the extensive disclosure and in light of the skill of those in the art, it is clear that the specification provides more than adequate enablement for the claimed invention, and Applicants therefore request reconsideration and withdrawal of the rejection.

**Rejections under 35 USC §102(e)**

Claims 1-7 stand rejected under 35 U.S.C. §102(e) as anticipated by US Patent Application Publication 2003/0215844 ("Chapsky"). Specifically, the Action asserts

that Chapsky discloses a method of detecting a target nucleic acid that is consistent with the steps of the claimed method. Applicants traverse the rejection.

As a threshold matter, the Federal Circuit has stated that for prior art to anticipate under section 102, every element of the claimed invention must be identically disclosed in a single reference. *Corning Glass Works v. Sumitomo Electric*, 9 U.S.P.Q.2d 1962, 1965 (Fed. Cir. 1989).

Applicants submit that Chapsky does not disclose every element of the claimed invention. At a minimum, Chapsky does not teach or suggest a method for detecting a target nucleic acid that includes ligating the first and second target specific nucleic acids together after the first and second target specific nucleic acids are hybridized to the target nucleic acid.

As noted in the specification on page 2, beginning at line 24, "The methods disclosed herein detect a DNA target as the result of ligation with two target-specific nucleic acids, which are ligated only in the presence of the nucleic acid target. The thus-ligated product is used to bridge a molecular motor and a detection probe." Such methods are not taught or suggested by Chapsky, and provide for extremely sensitive and specific detection, as detailed, for example, on page 26 lines 22-30 of the application.

Thus, Applicants respectfully request reconsideration and withdrawal of the rejection.

**Rejections under 35 USC §102(f)**

Claims 1-7 stand rejected under 35 U.S.C. §102(f) because it is asserted that Applicants did not invent the claimed subject matter. Specifically, the Action asserts that Chapsky discloses a method of detecting a target nucleic acid of interest using the same reagents as the claimed invention and since the inventorship of Chapsky is different than the claimed invention, inventorship is under question. Under 35 USC §102(f) a person shall be entitled to a patent unless he did not himself invent the subject matter sought to be patented. Applicants traverse rejection. As stated *supra*, Chapsky does not teach the presently claimed invention. Specifically, at a minimum, Chapsky does not teach ligating the first and second target specific nucleic acids together after the first and second target specific nucleic acids are hybridized to the target nucleic acid.

Thus, Applicants respectfully request reconsideration and withdrawal of the rejection.

If there are any questions or comments regarding this Amendment or application, the Examiner is encouraged to contact the undersigned attorney as indicated below.

Respectfully submitted,

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